Promoting Cardiovascular Education, Research and Patient Care

In This Issue

37  A Challenge
37  A Most-Deserved Honour
38  Executive Committe
40  Reports from Japan Meeting
41  Doctor Receives Volvos for Life
42  XVII Brazil Forum
43  Lasker Award for Development of Prosthetic Heart Valves
44  Indian First-in-man Trials
47  Turkey Symposium
49  John Madden's "Coach's Corner"
50  Mendel Symposium II
50  Dr. William Parmley
51  Dr. Bohdan Lewartowski
51  Dr. Sergio Dalla-Volta
52  Dr. Garrett Gross
53  Dr. Adolfo de Bold
55  3rd Congress in Serbia
56  State-of-the-brain-and-heart: Homo Obesus Bulgaricus
56  25th Brazilian Congress
58  World Heart Day
59  American Journal of Cardiovascular Drugs
60  Jordan — the Land of treasure and beauty
62  Jordan Symposium

A Challenge

Over the past 10 years, the Academy has built a base for international connectivity for promoting cardiovascular health. This has been achieved by establishing seven sections and holding a variety of workshops, symposia and conferences all over the world as well as having several publications and its own website.

Currently, the Academy is proposing to promote linkages among cardiovascular institutes and centres in the area of population health, clinical studies, scientific investigations, prevention and education for improving cardiovascular health. This could help facilitate exchanges of health professionals and foster collaborations. We wish to encourage all cardiovascular health professionals to send us suggestions for building this program.

For discussions, please contact me or any member of the Executive Committee. For your convenience, their contact information on pages 38-39.

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A Most-Deserved Honour

"HOUSTON — (October 2, 2007) Legislation authorizing a Congressional Gold Medal for Dr. Michael E. DeBakey, pioneering heart surgeon and chancellor emeritus of Baylor College of Medicine, is on its way to President George W. Bush for his signature.

The U.S. Congress today approved the bill that now will be forwarded to the president. U.S. Senator Kay Bailey Hutchison and U.S. Reps. Al Green, Michael Burgess and John Culberson led the efforts on the legislation.

‘After learning that I was going to receive this fine honor, the Congressional Gold Medal, my pride as a citizen of the United States of America is overflowing,’ DeBakey said. ‘It is a wonderful honor and I’m deeply grateful.’

The Congressional Gold Medal is considered the nation’s highest and most distinguished civilian award.

Continued on page 38
A Most-Deserved Honour  Continued from page 37

The first was awarded in 1776 to Gen. George Washington. It is awarded both for singular acts of exceptional service and for lifetime achievement.

‘Dr. Michael DeBakey has given so much to medicine and to the world at large,’ said BCM President and CEO Dr. Peter G. Traber. ‘It is most fitting that this high honor be given to him. Dr. DeBakey’s contributions to medical care, education and health care policy are legendary. He has touched not only the patients whose lives he directly saved but thousands of others who benefited from his surgical innovations. The Baylor College of Medicine family looks forward to celebrating this recognition with him.’

Hutchison, who has worked with DeBakey on many projects, spearheaded the efforts for the award. The Senate legislation passed in March. Green, Culberson and Burgess picked up the charge in the House. Final approval was given in the House this morning.

‘We are very grateful to Senator Hutchison and to Congressmen Green, Culberson and Burgess for their leadership in making this award possible,’ said Robert H. Allen, chair of the BCM Board of Trustees. ‘Dr. DeBakey is a true hero and very deserving of this recognition from the U.S. Congress. We are very proud of the contributions Dr. DeBakey has made, and continues to make, to Baylor College of Medicine.’

From Baylor College of Medicine web site

Editor’s note: Dr Debakey is a Fellow of the IACS and was the first recipient of the Academy’s most prestigious Medal of Merit in 2001. For an extraordinary article about his life, please look at our recent CV Network VOL 6 NO 2, page 31

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Bush signs bill giving Dr. Michael DeBakey top civilian honor
On Tuesday, October 16, 2007 Famed Houston heart surgeon Michael DeBakey has been awarded the nation's top civilian honor – the Congressional Gold Medal. President Bush finalized the award Tuesday by signing a bill approved recently by the Senate and the House of Representatives.
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The 6th Annual Meeting of IACS Japan Section

The 6th Annual Meeting of the International Academy of Cardiovascular Sciences (the 30th Japanese Working Group for Cardiac Structure and Metabolism) was held on July 14-15th, 2007 at the Paruru Plaza, Kyoto, Japan. Prof. Akira Matsumori, MD, PhD, FACC, FAHA, FESC, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine chaired the meeting.

The meeting was fruitful and successful, with 110 basic scientists and clinical researchers gathering from all over Japan to discuss recent topics in the field of cardiovascular medicine.

Dr. Peter Liu, University of Toronto and Canadian Institutes of Health Research, gave a special lecture titled “Interplay between cardiovascular remodeling and metabolism in heart failure.” Four invited lectures were given by experts in basic science from outside of cardiovascular field.

1. Dr. Akihiko Yoshimura, Division of Cellular and Molecular Immunology, Medical Institute of Bioregulation, Kyushu University. “Molecular mechanisms and functions of the SPRED/SPROUTY family proteins: Negative regulators for the RAS/ ERK pathway.”

2. Dr. Jun-ichi Miyazaki, Division of Stem Cell Regulation Research, Osaka University Graduate School of Medicine. “Regeneration of pancreatic beta cells in vitro and in vivo.”

3. Dr. Hidetoshi Inoko, Division of Molecular Medical Science and Molecular Medicine, Tokai University School of Medicine. “Genome-wide scan of genes for multi-factorial diseases such as common diseases by association analysis using microsatellites.”

4. Dr. Hajime Kubo, Department of Surgery, Kyoto University Graduate School of Medicine. “Expanding world of lymphangiogenesis: The role of lymphatics in diseases.”

All four lectures were excellent, impressive, and instructive, and made a great impact on the audience.

Abstracts sessions were held on the topics of regenerative medicine, cardiac function, signal transduction, calcium signaling, atherosclerosis, myocardial ischemia, cardiomyopathies, and heart failure. Each of the 30 presentations was high in quality. Sixteen abstracts were submitted to the Competition for Young Investigators Awards. Dr. Kento Tateishi (Department of Experimental Therapeutics, Translational Research Center, Kyoto University Hospital, and Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine) won the first prize of this competition. His presentation was “Clonally amplified cardiac stem cell antigen-1 signaling for efficient cardiovascular regeneration.”

The next meeting will be held on July 12-13, 2008 in Tokyo under the chairmanship of Dr. Satoshi Kurihara, Jikei University School of Medicine, Tokyo.

3rd Young Investigator Award of IACS Japan Section

At the 7th Annual Meeting of IACS Japan Section in Kyoto, July 14-15, 2007, the Japan Section of IACS selected Dr. Kento Tateishi, an excellent young researcher, for the 3rd Young Investigator Award. Siemens. Asahi Med. Techno Ltd. in Japan, sponsors this Young Investigator Award.

At this meeting, 16 candidates from 16 different University departments were recommended and Dr. K. Tateishi received the Award.

He is researching at the department of Experimental Therapeutics, Translational Research Center, Kyoto University Graduate School of Medicine. He was born in Kyoto, Japan. After graduating from School of Medicine, Kyoto Prefectural University in 1998 (MD), he was trained as an intern in internal medicine. From 2000 to 2006 he was a postgraduate student of Kyoto Prefectural University School of Medicine and worked in the department of Exp. Therapeutics, Translational Research Center, Kyoto University Graduate School. He received his PhD in March 2007.

His presentation, for which he earned the Young Investigator Award, was: “Clonally amplified cardiac stem cells are regulated by stem cell antigen-1 signaling for efficient cardiovascular regeneration”. Cardiac stem cells (CSCS) from the adult heart can differentiate into functional cardiomyocytes; however, the definite surface markers to identify the entity of CSCS and the molecular mechanisms regulating their growth have remained unknown. Dr. Tateishi demonstrated a single-cell analysis to isolate CSCS from the adult hearts and investigated the signals required for their proliferation and survival.

Clonally proliferated CSCS express stem cell antigen-1 (Sca-1) and are associated with telomerase reverse transcriptase (TERT). Using GFP-reporter transgenic mice under the control of TERT promoter, he demonstrated that TERTGFP+ fractions from the heart were enriched for the cells expressing Sca-1. Targeting Sca-1 transcripts in CSCS showed that CSC proliferation and survival required Akt signaling to upregulate the secreted paracrine effectors to limit cardiac apoptosis in ischemic myocardium. Thus, Sca-1 might be an essential component that promotes CSC proliferation and survival to facilitate cardiovascular regeneration after CSC transplantation.
Doctor Receives Volvos for Life

A local hero from the Detroit area today is receiving a “thank you” to last a lifetime: a complimentary new Volvo car every three years for the rest of his life.

Earlier this year, celebrity judges named Dr. Ingida Asfaw, “America’s Greatest Hometown Hero” in the fourth annual Volvo for life Awards, the nation’s largest search for and celebration of everyday heroes, with Volvo providing $1 million in contributions in honor of local heroes. Dr. Asfaw is an Ethiopian-born heart surgeon who kept a half-century promise to himself by creating an international coalition called the Ethiopian North American Health Professionals Association (ENAHPA) to address his homeland’s medical crises.

Launched in 2002, the Volvo for life Awards calls for people nationwide to nominate a local hero they know doing the extraordinary in the areas of safety, quality of life or environment at www.volvoforlifeawards.com. Since June 2005, Volvo has received more than 4,341 nominations, including Dr. Asfaw’s and 49 others from Michigan, for the 4th Annual Volvo for life Awards. In February, Volvo selected three winning heroes in each category.

Judges Hank Aaron, Sen. Bill Bradley, Caroline Kennedy, Sir Richard Branson, Eunice Kennedy Shriver, Val Kilmer, Maya Lin, Paul Newman, Dr. Sally Ride and Hope Bevilhymer (3rd Annual Volvo for life Awards winner) then selected the overall category winners, who received a $50,000 charitable contribution. At a gala ceremony in New York this past April, judges announced Dr. Asfaw as the winner in the quality of life category and also unveiled him as the overall grand winner and a recipient of a Volvo car every three years for life.

For his first car choice, Dr. Asfaw selected the 2007 Volvo XC90 V8. Today at a lunchtime ceremony at Suburban Volvo in Troy, Mich. attended by Dr. Asfaw’s friends, family and associates, the retailer and executives from Volvo Cars of North America presented Dr. Asfaw with the keys to his new car.

“Every year I am touched by the amazing stories and thousands of nominations we receive through the Volvo for life Awards,” said Anne Belec, president of Volvo Cars of North America. “Dr. Asfaw stands tall as a man who has devoted his energy and skills to addressing a devastating crisis in his homeland. It’s an honor for Volvo to help him advance his cause.”

The 5th Annual Volvo for life Awards already is underway. Volvo has named 250 extraordinary heroes nationwide -- five per state -- as semi-finalists. Now, for the first time, individuals can vote for their favorite heroes at www.volvoforlifeawards.com through Feb. 4, 2007. In March, Dr. Asfaw will join celebrity judges in selecting next year’s winning heroes, to be honored April in New York.

About Dr. Asfaw

At the young age of 16, Asfaw departed from his hometown in Ethiopia determined to study medicine in the United States and in return put an end to the lack of a national healthcare program. Now, at 68 years of age, he has kept his promise of someday returning to Ethiopia with helping hands.

In 1999 Dr. Asfaw started ENAHPA and encouraged others to join him in treating the people of Ethiopia. In a country where the ratio of physicians to population is 1 per 100,000, the idea of a healthcare system was nonexistent and Dr. Asfaw’s dream was to change just that. With support from over 500 medical and non-medical professionals and volunteers from the United States, Canada, China and South America, a sense of hope has been returned to the people of Ethiopia. ENAHPA has led the volunteers through mission trips and other social initiatives to address the healthcare crisis by donating their time and service.

This renowned surgeon along with his team of ENAHPA volunteers has performed nearly 100 surgical procedures; conducted advanced training for 250 Ethiopian healthcare professionals and donated 32,400 books; provided lifesaving medical equipment; instruments and supplies to several specialized hospitals, three universities and a leprosy research training center. Now over 500 AIDS orphans are being cared for by a newly created program by Dr. Asfaw, which supports a grassroots Ethiopian organization to provide the patients with the medical care they need.

Now residing in Metro Detroit, working as cardiovascular surgeon at: Sinai-Grace Hospital, St. Joseph POH North Oakland Medical Center, Huron Valley Hospital, Harper Hospital and Crittenton Hospital Dr. Asfaw has taken on another challenge working as a clinical professor of surgery at Wayne State University. Dr. Asfaw is also the chairman of cardiothoracic surgery at Trinity Heath-St. Joseph Mercy Oakland and chief executive officer of Cardiothoracic and Vascular Surgeons of Michigan.

About Volvo for life Awards

The Volvo for life Awards was launched in 2002 to recognize and celebrate local hero’s nationwide. For more information or to vote for the fifth annual Volvo for life recipient please visit our website at www.volvoforlifeawards.com. Who would you give a Volvo to? Join us in the search for the 2007 Volvo for life recipient by simply submitting a nomination and voting for your local hero.

For photos and more information on the Volvo for life Awards: www.volvocars-pr.com
INTERNATIONAL CONGRESS ON CARDIOVASCULAR SURGERY

12 COUNTRIES
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153 SPEAKERS

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www.isciforum.com
Lasker Award for Development of Prosthetic Heart Valves

If you’ve ever used a hand-held pump to inflate a bicycle tire, you know that pumps need two valves—one to permit air to enter on the intake stroke, and the other to permit air to exit during expulsion. Our hearts are no different. Each of the two pumping chambers has two valves—one for intake and one for expulsion. Heart valves are remarkably resilient. Over a human lifetime they open and close 3 billion times, allowing 50 million gallons of blood to pass. When they close, they prevent the backflow of this deluge. It’s no wonder that heart valves wear out.

They can wear simply with age, or they can fail early in life as a result of birth defects, or diseases like rheumatic fever and bacterial infections. Disease can constrict the valve, blocking the flow of blood, or it can render the valve leaky, permitting devastating back-flow. Often a single valve can suffer both problems.

Before 1960, disease of heart valves meant certain death—either catastrophically or slowly when the heart failed as it tried to overcome the inefficiency in pumping blood. All of that changed on a single day—September 21, 1960—in a surgical suite in Portland, Oregon. There, Albert Starr implanted the first successful artificial heart valve in a 52-year-old man who was literally on his death bed. In childhood, this man had suffered from rheumatic fever, which had fatally damaged his mitral valve, the one that admits blood into the left ventricle. Earlier, surgeons had tried to repair the valve, but the valve was beyond repair. Without a new valve this man would surely die. Starr’s artificial valve was a remarkable success and the man lived normally for 10 years until he was killed by falling off a ladder.

The story that led to this medical miracle began two years earlier when Lowell Edwards, a 62-year-old inventor with experience in fluid dynamics, walked into Starr’s office and proposed the invention of an artificial heart valve. Starr was a young surgeon, fresh out of residency, who had trained at Columbia College of Physicians and Surgeons right here in New York. After further training at Johns Hopkins, in 1957 Starr moved to Portland to start a clinical and research program in the brand new field of open heart surgery. He took Edwards up on his challenge, and the two set out to invent a heart valve. For the next two years they experimented intensely on dogs. After trying other designs, they eventually chose a caged ball valve like one that was invented as a wine bottle stopper in France a century before. It didn’t look like nature’s solution, but it had two properties that made it ideal: First, it did not damage the blood cells as they passed through it; and second, it was partially resistant to clotting.

Starr and Edwards made careful calculations of the size of the opening and the physical and chemical properties necessary for the ball and its cage, and then they tested it by implantation into dog hearts. Their biggest problem was blood clotting. When blood touches a foreign surface it triggers a cascade of enzymes that quickly make the blood congeal. Clotting is essential to life. But it creates an enormous problem when one places a foreign object in the bloodstream. Fortunately, Starr and Edwards could take advantage of inventions made for other reasons. First, they made the ball from silastic, a combination of silicone and plastic invented by Dow Corning scientists in the 1940’s as a sealant. When exposed to blood, silastic is relatively inert. Second, they could block clotting by using a new oral anticoagulant, coumadin, that had been invented 10 years earlier as a rat poison.

Of course, the very idea of heart valve replacement could not have been envisioned without the pioneering work of John Gibbon, who in 1953 performed the first open-heart surgery using a heart lung machine. Gibbon received the Lasker Award in 1968. The world also owes a debt to Charles Hufnagel, a surgeon who had earlier implanted a caged ball valve in the aorta of a patient with aortic regurgitation.

In addition to their creativity, skill and courage, Starr and Edwards are noteworthy for their unselfish efforts at teaching other surgeons how to duplicate their success, and their diligence at keeping track of their patients and reporting their failures as well as successes. By the present time, modifications of the original ball valve have been made, and new approaches have been pioneered, as we will hear in a moment. Nevertheless, it is proper to consider Albert Starr and Lowell Edwards as the fathers of artificial valves, and millions of patients literally owe their lives to them. Unfortunately, Lowell Edwards passed away in 1982. Otherwise, he would surely have shared today’s Award.

The Starr-Edwards valve broke the ground, but it left a problem. The recipients were committed to taking anticoagulants for the rest of their lives. The dose must be adjusted carefully. If the dose is too low, clots form on the valve, triggering strokes and other catastrophes. If the dose is too high, blood will not clot and fatal bleeding will occur. Now the scene shifts to Paris and another young surgeon, Alain Carpentier. As a surgery resident in the early 1960s, Carpentier observed a young man who had received a Starr-Edwards valve and had suffered a stroke caused by a blood clot. Carpentier decided to devote himself to finding a valve that would not clot.
Lasker Award for Development of Prosthetic Heart Valves – continued

Previous work had shown that animal valves could be implanted into human hearts, and they did not clot. But there was a problem. After a few months the animal valves deteriorated. Through brilliant deduction Carpentier discovered that the valves would function much longer if they were first treated with glutaraldehyde, a chemical that crosslinks the proteins of the valves, reinforcing the structure much like bridges are supported by cross-linked triangular beams. Glutaraldehyde also reduces the tendency of the valve to stimulate immune rejection. Carpentier obtained valves from pigs, treated them with glutaraldehyde, and attached them to a ring that kept them expanded and allowed them to be sewn into the human heart. After this treatment the pig valve was no longer natural—it was a new structure that Carpentier called a bioprosthesis. The result was dramatic. Bioprosthetic valves are efficient and long-lasting. Moreover, the patients do not require anticoagulants. The valves work especially well in older patients.

Today, the majority of valves implanted into people above age 60 are Carpentier valves. But Carpentier did not stop with bioprostheses. He realized that sometimes the valve did not need to be replaced. He developed ingenious methods to reinforce and repair the patient’s own valve. His repair methods revolutionized cardiac surgery.

Another of Alain Carpentier’s contributions deserves recognition. He has used his skill, his influence and his personal wealth to bring the benefits of cardiac surgery to thousands of poor people in developing countries. In 1992, he founded a hospital in Vietnam that performs 1000 open heart surgeries every year. As a Director of the World Heart Foundation, Carpentier has brought the benefits of cardiac surgery to many nations in Africa. But Dr. Carpentier doesn’t only help the poor. He saves some time for the rich. Last year he performed emergency surgery that saved the life of a prominent New Yorker, Charlie Rose, whose mitral valve failed while in Syria.

As I look back at the enormous contributions of Starr and Carpentier, I am struck by the confluence of prior advances that they brought together. Of course there was the heart-lung machine. But this machine could not have been invented without something as mundane as silastic tubing. Coumadin was a rat poison. Glutaraldehyde came from leather tanning and electron microscopy. And no surgical advance could take place without medical discoveries like antibiotics, methods to manage fluid and electrolytes, selection of blood donors who are compatible immunologically, and treatment of heart arrhythmias. Technology expands geometrically. Each advance multiplies the advances before it. We live on the ascending limb of this expansion where unrelated advances can be brought to bear on a single problem like valvular heart disease. And all of this happened before Google, the limitless library that allows every inventor immediate access to all prior knowledge. What a playground for creative minds like those of Starr, Edwards and Carpentier. Let us all act to insure that the human benefits from this age of enlightenment do not fall victim to those who would return the world to ignorant darkness.

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First-in-man Clinical Trials in India

Emerging trends of Clinical Research in India:

Developing a new drug today estimates to almost $800 million to nearly $2 billion, with this cost continuing to rise. The total global pharmaceutical R&D expenditure has been increasing by more than 11% every year since 2001 to surpass a colossal $60 billion this year. Pharmaceutical companies are therefore actively searching for solutions to reduce costs. Clinical trials are of particular concern, since they can account for almost two thirds of the costs of developing a new drug. FDA regulations require more and more results to approve new drugs but contract and budget delays and patient recruitment difficulties result in 94% of all US trials being delayed over a month, with each additional day leading to $1 million dollars lost in revenue.

Recent trends have seen clinical research segment emerging outside US boundaries and getting established in Europe and Asia. India and China share the major chunk of benefits from a rise in clinical research activities in Asia. A vast, unwieldy population, a plethora of diseases, and rampant poverty – was the picture India presented to the outside world till a while ago. But these days the fact that India has the largest pool of patients suffering from cancer, diabetes, cardiovascular diseases and other maladies is leading the country to become the global hub of clinical trials outsourcing. Pfizer initiated this trend with a small clinical research unit in Mumbai in 1995. A decade later, all global pharmaceutical companies such as Novo Nordisk, SanofiAventis, Novartis, GlaxoSmithKline and Eli Lilly started conducting clinical trials across various Indian cities.

Why India:

India, being a “low-cost countries” is becoming increasingly attractive as clinical trial outsourcing destination. It has the largest pool of patients suffering from the developing world’s most common diseases. The World Health Organization estimates that in 2010 six cardiovascular patients out of ten will be Indian, with developing urbanization and growing life expectancy sustaining this phenomenon. While less than 5% of the patients in US are willing to participate in clinical trials, Indian patients see trials as a unique opportunity to receive extensive healthcare, thus allowing 5 to 6 times faster recruitment. Most patients are treatment-naive and their genetic diversity are additional assets of the Indian population. Moreover, India has an attractive number small and large, general and specialty hospitals, medical colleges, a long-established pharmaceutical industry and a large pool of highly skilled English speaking healthcare professionals; many of whom are also trained overseas. All this enables generation of well accepted, good quality, auditable data at
very low costs. A 2004 RaboBank India study estimated that Phase II and III trials in India can cost 60% less than in the US. The 2004 A. T. Kearney's report rates India at the top for offshore location attractiveness index. The 2005 A.T. Kearney's countries attractiveness index for clinical trials, ranked India second. The index was based on patient pool, cost efficiency, regulatory conditions, relevant expertise and infrastructure and environment.

Insufficient regulatory infrastructures, experience to monitor the situation tightly, ethic dilemmas in patient recruitment and a history of little-protecting IP laws cautions the investors' interest. There are indications towards the growing shortage of experienced clinical research professionals as well. However, the recent government measures taken boost the promising market. In 2005, an amendment to the Schedule Y of the Drug & Cosmetics Act defined Indian guidelines for GCP based on the International Conference on Harmonization's guidelines. In that same year the controversial Patent Act was amended, strengthening intellectual property protection to a point considered as beyond the WTO's requirements by a few. In December 2006, the Drugs Controller General of India (DCGI) has simplified the process for gaining regulatory approval for global clinical trials. Protocols already approved in a selected number of countries including US, UK and the EMEA will be accepted which would shorten the regulatory approval delays. Recently, in April 2007 all services carried out by the Indian contract research and clinical trials industry were exempted from a previous service tax, allowing even more competitive costs.

All these changes should sustain the exploding Indian clinical trials' market. A confederation of Indian Industry Study evaluated in 2002 that clinical trials in India generated $70 million that year and predicted that it would grow to $200 million by 2007 and to between $500 million and $1 billion by 2010. In June 2007, the US National Institute of health clinical trial registry listed 256 trials recruiting or due to recruit in India, 33 of which had cardiovascular disease as a condition – and there are certainly many more unregistered trials.

More and more players are appearing, from international companies setting up local divisions in India to growing Indian companies. Simultaneously, numerous Clinical Research Organizations have appeared, including well-known names such as Quintiles, ClinTec, Covance, Pharm-Olam, Pharnanet, Omnicare, PPD, Icon, Chiltern and Kendle. Indian CROs have also been mushrooming, including Lambda Therapeutics, ClinWorld, ClinInvent, ClinRx, Pharmaintel and Synchron.

Almost all the top names in the pharmaceutical world have zeroed-in on India, setting up clinical trial facilities in major cities, especially Hyderabad and Ahmedabad.

Ahmedabad – A promising metropolitan for cardiovascular diseases:
Ahmedabad is India’s sixth largest city with a population of 5 million. Leading Indian pharmaceutical companies such as Zyus Cadila are based in the city, taking advantage of its soaring economical growth and renowned entrepreneurial spirit. The largest Indian CRO, Lambda Therapeutics is headquartered in Ahmedabad besides Synchron and Accutest. The city is also attractive to foreign interests; the first global CRO establishment in India was the opening of Quintiles’ Ahmedabad office. Furthermore, the important health infrastructure of the city is a definite asset, with numerous hospitals and clinics, 3 renowned medical colleges and the recently-opened Indian Clinical Research Institute Ahmedabad campus. In the cardiovascular arena, Ahmedabad proposes more than 30 hospital cardiology units and more than 10 cath-labs, most of which equipped state of the art and the U.N. Mehta Institute of Cardiology and Research Centre.

First-in-man Clinical Trials at Ahmedabad:
First-in-man drug studies are currently restricted in India, but avenues are open for medical devices. As an example to this, two first-in-man medical device trials were successfully accomplished by the Team of Cardiologists of The Heart Care Clinic at Ahmedabad led by Dr Keyur H Parikh. This center was one of the three centers across the world, participating in this pilot trial. The medical device studied was a stent-like device designed to establish coronary sinus (CS) narrowing and to elevate CS pressure in patients with refractory angina.

Patients with refractory angina pectoris also known as 'no option' patients, are often having severe diffuse coronary artery disease and are not candidates for further revascularization by coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). These patients continue to be asymptomatic in spite of ongoing pharmacological therapy. The estimated 1- and 3-year mortality rates for these patients are 1% to 5%, and up to 24%, respectively. A considerable number of therapeutic strategies for treating severe chronic angina have been investigated, however, they all have only limited feasibility and none of them has become a widely used therapy.

Increased CS pressure can reduce myocardial ischemia by redistribution of blood from nonischemic to ischemic territories. The study evaluated safety of this stent (Reducer®; Neovasc Medical Ltd, Israel) as a potential alternate therapy for patients with refractory angina. The device was intended to establish CS narrowing and elevate CS pressure. In preclinical experiments, implantation of the Reducer was safe and was associated with improved ischemic parameters. In the present study, the safety and feasibility of the CS Reducer was evaluated in fifteen patients with refractory angina who were not candidates for revascularization.

Ten out of the fifteen patients enrolled across other parts of the world, were studied at the Ahmedabad center between March – September 2005. Ethics committee approval was sought before the initiation of the study. The study was conducted adhering to ICH-GCP guidelines and all patients gave written informed consent for their participation. The devices were percutaneously implanted and all the patients were followed for over one year. All procedures were completed successfully. No procedure-related adverse events occurred during the periprocedural and the follow-up periods. Implantation of this device led to improvement in the angina score, reduction in stress-induced ST-segment depression and extent & severity of myocardial ischemia in these patients.12 Thus, this novel device appeared safe and feasible with clinical improvements in these patients, who were otherwise with 'no options'.

The second pilot study evaluated an implantable device for non-invasive monitoring of pulmonary artery pressure in heart failure patients. This study was also conducted by the team of Cardiologists of The Heart Care Clinic, Ahmedabad under the principal supervision of Dr Parikh. This was the only center across the world to conduct this first-in-man study. The system evaluated consists of a
miniature implant and a desktop monitoring system (ImpPressure®; Remon Technologies, Israel) to monitor pulmonary artery pressure non-invasively in patients with Congestive heart failure (CHF).

CHF is a major cause of mortality, morbidity, and hospitalization worldwide. The Left Ventricular End Diastolic Pressure (LVEDP) is a critical hemodynamic parameter, which is the basis for most decompensation events. The LVEDP is obtained clinically from the Pulmonary Capillary Wedge Pressure, which correlates with the Pulmonary Artery Diastolic Pressure (PADP). Thus, frequent, readily available, monitoring of Pulmonary Artery Pressure (PAP) and PADP should supply the necessary feedback loop for appropriate therapy. While cardiac catheterization is the most accurate way to define the hemodynamics, the invasive nature of this procedure limits its use. Clinical deteriorations are often preceded by elevation of left ventricular filling pressures and increased fluid volumes in the lung and noninvasive detection of these changes might be helpful for patient care. The noninvasive detection of hemodynamic abnormalities before clinical deterioration occurs might be helpful to improve care and hence is currently the new target research. Hence, the purpose of this first-in-man study was to examine the feasibility of repeated PAP determinations using a newly developed acoustic wireless implanted communication system. Pre-clinical study with this device in 10 pigs was conducted to establish ability of PAP determination from the Implant using wireless acoustic communication.

The clinical study enrolled ten NYHA class III/IV heart failure patients in July 2005 after the approval of the Institutional Ethics committee. ICH-GCP principles were adhered throughout the conduct of the study and all patients gave written informed consent for participation. The device was implanted using right heart catheterization and accuracy of PAP measurement was determined by comparison with simultaneous pressure monitoring forming a Control Millar catheter. The device was successfully implanted in the PA using right heart catheterization in all the patients. There were no implantations or other device-related complications. Pulmonary artery pressure tracings were repeatedly obtained from all implants. All the patients were systematically followed for over one year. This pilot study successfully demonstrated the feasibility of acoustic wireless communication with a miniature implanted sensor for repeated pulmonary artery pressure monitoring.

CHF patients show diurnal variation in hemodynamics with nocturnal worsening of symptoms. The reduction of exercise capacity with early occurrence of fatigue and dyspnoea is a hallmark of HF syndrome. Further, management of the CHF patient is a complex task that involves titration of several drugs, which may interact with each other, and trigger undesired results. Therefore, following this successful implantation and functioning of the device, we evaluated the diurnal variation, exercise induced variation in PAP and effect of metoprolol on the PAP using non-invasive monitoring by this device. Following the implantation, all patients were loaded with metoprolol 25mg/day and then uptitrated till 200 mg/day as per MERIT-HF criteria. Diurnal variation was done by measuring PAP every two hours during day and every three hours during night at baseline, and after 100mg/day and 200mg/day metoprolol. TMT was done before each uptitration. Metoprolol uptitration caused a slight rise in PAP.We did observe a nocturnal rise in PAP in these patients, but this rise was blunted eventually by uptitration of metoprolol to the target dose. PAP rose significantly after TMT in all patients. Metoprolol uptitration improved the exercise time and exercise capacity without any significant rise in PAP. Thus, the non-invasive measurement of PAP with this novel device, indeed assisted daily monitoring of hemodynamic changes and may therefore guide the adjustment of therapy in these patients.

Clinical development is complex and highly sensitive to globally-accepted quality, compliance, GCP and ethics standards. Although clinical development in India still relies heavily upon its cost-effectiveness to attract outside firms, there is increased awareness of quality requirements. Both these first-in-man studies demonstrated new therapeutic and diagnostic applications for the patients with end stage diseases. The feat of such continuing trials in India, further assures the quality along with low cost benefits for the extra-ordinary proliferation of companies and research units in coming years. Moreover, India’s IT strength provides opportunities to capitalize on clinical data management much more quickly than clinical trials, where quality, compliance, drug safety, risk management and regulatory aspects dominate. While offering promising new clinical trial outsourcing opportunities, India still needs to address many challenges to meet global standards.

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SPONSORED by INTERNATIONAL ACADEMY of CARDIOVASCULAR SCIENCES
Many people say that John Madden was born to coach, and that may be true. In fact, John has enjoyed several successful careers, all centering around the world of sports. He is the well-known former NFL football head coach who led the Oakland Raiders to victory in Super Bowl XI. He has authored several best-selling books. And he has received 13 Emmy Awards over 20 seasons as a popular TV sports broadcaster. Currently, John Madden is seen and heard weekly on the “Sunday Night Football” television program. When he isn’t traveling the country from assignment to assignment in his Madden Cruiser bus (John refuses to fly), John resides with his wife, Virginia, in the San Francisco Bay Area. The couple has two sons and several grandchildren.

John Madden Speaks of the Madden Family’s Experience With Vascular Diseases

“While in her mid-40s, my wife, Virginia, developed a health condition that, frankly, at the time we didn’t know anything about. At first it was misdiagnosed. Fortunately, we ended up going to the right doctor who correctly identified the problem - a blocked carotid artery, the main blood vessel that leads through the neck to the brain - a deadly condition if not treated. Today, Virginia is fine and our family is better informed. We learned her condition was a vascular disease. And we learned that vascular disease is a silent killer.

Virginia’s condition opened our eyes to vascular diseases, a world of serious medical conditions affecting arteries and veins that, like us, very few people are familiar with. It’s true people have heard about heart attacks, but they may not know what causes them, even though a heart attack is usually the result of a problem with an artery. And people have heard about strokes which are often called “brain attacks” because they affect the brain the way heart attacks affect the heart, through a problem or blockage in an artery. There again, people may not connect the term “stroke” to vascular disease, but they’re one and the same.

Do you know that almost one in two women over age 55 dies from vascular illness? Do you know, for example, that every thirty seconds, someone in the U.S. dies from a vascular disease? And, perhaps most importantly, do you know that vascular disease is not just a condition affecting women or older folks, but is one that can affect people across all ethnic groups and ages? You see, not only did Virginia have her problem, but our grandson, Sam, has a vascular disorder, similar to the condition that afflicts Casey Martin, the talented golfer who can’t walk the course and needs a golf cart to get around. Thanks again to excellent care from outstanding vascular specialists, Sam’s prognosis is excellent.

The fact is vascular diseases are life-threatening, potential killers that can strike anyone at any age at anytime. Cardio-vascular (heart and blood vessel) disease is the leading cause of death in the United States - one million people die from it annually. Other vascular diseases, excluding the heart, account for a third of a million deaths and cripple half of the survivors. These diseases include stroke, abdominal aortic aneurysm, high blood pressure and kidney failure, peripheral vascular (arterial) disease and vein (venous) disease.

But there are dedicated scientists and doctors who are trying to get to the bottom of these diseases. The non-profit Pacific Vascular Research Foundation (PVRF) supports innovative research into the causes and treatment of vascular diseases, educates physicians and patients, and conducts ongoing public outreach programs to alert the public about this serious health threat. In fact, PVRF’s President, Dr. Ron Stoney, is the vascular surgeon who operated on my wife, Virginia, and may well have saved her life.

PVRF supports a scientific research facility, the Pacific Vascular Research Laboratory, located at the University of California, San Francisco (UCSF), and award grants to medical academic scientists engaged in independent, breakthrough research into life-saving treatments for vascular disease.

The Maddens are doing what we can to help people learn more about vascular disorders. I think it’s like preparing a team for any upcoming game or challenge - the more you know about your potential opponent, the better prepared you are and the greater the likelihood you’ll be successful.
Joint meeting of the Japan and European Sections of the International Academy of Cardiovascular Sciences organized by the Centre of Cardiovascular Research, Institute of Physiology, Academy of Sciences of the Czech Republic, Prague

Local Organizing Committee:

Scientific program:
- Gene and cell therapy
- Genetic aspects of
  - Cardiac development
  - Experimental models
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- Hypertension
- Atherosclerosis
- Coronary artery disease
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As a continuing feature of CV NETWORK ONLINE, to follow are articles about Fellows of the Academy: Dr. William Parmley, Dr. Garrett Gross, Dr. Sergio Dalla-Volta, Dr. Bohdan Lewartowski and Dr. Adolfo J. deBold. We invite all Fellows to submit such information.

Dr. William Parmley

Dr. Parmley was born in Salt Lake City, Utah in 1936. His education included an AB from Harvard College in 1957 (summa cum laude in physics), and an MD degree from Johns Hopkins University School of Medicine in 1963. He obtained his internal medicine training on the Osler Medical Service at Johns Hopkins and then spent two years at the National Institutes of Health in Bethesda, Maryland, under the tutelage of Eugene Braunwald and Ed Sonnenblick. His cardiology training was completed at the Peter Bent Brigham Hospital and Harvard under the tutelage of Richard Gorlin and Ed Sonnenblick.

He then served for 4 years as Associate Chief of Cardiology at Cedars Sinai Medical Center in Los Angeles, California, under Jeremy Swan. In 1974 he became Chief of Cardiology at the University of California San Francisco School of Medicine, a position he held for 23 years.


His honors include Phi Beta Kappa from Harvard; Alpha Omega Alpha from Johns Hopkins; Distinguished Fellow and Master, American College of Cardiology; Distinguished Service Award, Collegium Aescullapium; Brigham Young University, Academy of Medicine.

He served on the ABIM subspecialty Board on Cardiovascular Disease from 1981 to 1987 and as its chairman from 1985 to 1987. He served on several review boards including the VA, NIH, and FDA. He has served on many Committees of the American College of Cardiology, including being its President from 1985-1986. He was a Visiting Professor over 40 times at various institutions. He is an author or coauthor of about 350 scientific publications, two textbooks, and 125 editorials.

“As I reflect back on my career in cardiology, I am grateful for the mentorship I received from more senior colleagues who helped me in my career. I have also tried to stimulate younger colleagues to have a successful career in academic medicine. That perhaps is one of the best ways for us to payback our thanks for all we have received in our own careers. Passing the torch to the next generation is clearly our obligation and our opportunity.

After retirement in 2003, I have continued to have the opportunity to teach and help others, in this case in Africa. I have the administrative responsibility for the affairs of our Church (Church of Jesus Christ of Latter-day Saints) in 30 countries in southeast Africa. We have extensive missionary, humanitarian, educational, literacy, employment, and welfare programs in these countries. AIDS and Malaria are two of the major medical problems we face, and we are engaged in preventive educational efforts. We have dug scores of bore holes to provide clean water, especially out in the villages. Although these activities are quite different from my career in cardiology; in many ways they are more satisfying. The need here is so great that the personal satisfaction level is also great. We anticipate a total of 5 years in this assignment in Africa, which has now become our second home. My wife and I have certainly learned that service to others is the key to personal happiness.”

Dr. Bohdan Lewartowski

Dr Bohdan Lewartowski, MD., PhD was born in Warsaw (Poland) in 1929. During the Second World War he served in Polish Underground Resistance Forces (Home Army) and from the 10th of August 1944, till the 3rd of May 1945, he was a prisoner in the Nazi German Concentration Camp Sachsenhausen. After the war, he came back to Warsaw where he obtained his scientific degrees (MD, PhD) and specialization in internal diseases at the University Medical School of Warsaw. He received his postdoctoral training in the Department of Human Physiology of the Medical School in Warsaw and in the Department of Experimental Cardiology (headed by Prof. Dirk Durrer) of the University of Amsterdam. In 1967, he obtained a degree of the habilitated doctor (docent) and moved to the Medical Center of Postgraduate Education (MCPE) in Warsaw where he organised the Department of Clinical Physiology (headed by him until his retirement in 1999). From 1972 until 1982 he was a Deputy Director and Director of MCPE, which is an academic institution heading the nation-wide system and providing facilities for specialization and continuing postgraduate education of Polish medical doctors. In 1978, he obtained the title of Professor in Medical Sciences. During 1988/89, Dr Lewartowski was the Visiting Scientist in the Laboratory of Cardiovascular Sciences (headed by
Sergio Dalla-Volta

Sergio Dalla-Volta was born December 30th 1928. He pursued classical studies in high school; graduated in Medicine, University of Padova (Padua), Italy 1952; Fellow in Cardiology, University of Padova 1954; Assistant Etranger, Hopital Boucicault Paris, France 1954-55; Research Fellow, Karolinska Institutet (Medical School), Stockholm, Sweden 1955-56; Investigador (Research Fellow) Instituto de Cardiologia de Mexico 1956-58; Assistant Professor of Medicine (Cardiology) University of Padova 1959-62; Research Fellow, Dpt of Physiology, University of Mississippi in Jackson, USA, 1962; Associate Professor Cardiology, University of Padova 1962-64; Associate Professor of Cardiology, Columbia University, New York, NY, USA, 1965-68; Professor of Cardiology, University of Padova, 1969-75; Associate Professor of Pediatric Cardiology, Harvard University, Boston, MA, USA, 1975-78; Professor of Cardiology and Head of Dpt of Cardiology, University of Padova 1979-2003; Professor of Cardiology, University of Spalato/Split, Croatia 1998-2006; and Distinguished Professor of Cardiology, University of Padova, since 2003.

He has been Howard-Gilman Visiting Scientist, Cornell University, New York, NY, USA, November 2001; Member of twelve international Societies of Cardiology, among them the fellowship of the AHA and Silver Medal of AHA, 2004; Recipient of the Hans-Peter Krayenbuhl Award of the International Academy of Cardiology, Los Angeles, CA, USA, 2003; Fellow of the International Academy of Cardiovascular Sciences, Winnipeg, MA, Canada 2003; Member-elect of the Emam and PVA Club, Osaka, Japan, 2006.

Author or Co-Author of 500 scientific papers, with impact factor of more than 550 (many papers published in New England Journal of Medicine, Circulation, Cardiology, Archives des Maladies du Cœur, etc.); Author and Editor of six books of Cardiology and Editor in Chief of the international “Hot Topics in Cardiology”; Member of the Scientific Board of international journals “Cardiology”, Basel Switzerland, from 2204 and “Archivos del Instituto de Cardiologia de Mexico”, Mexico, (1998-2004).

Participation of several international congress of Cardiology, among them the AHA, ESC and other European and American meetings. His fields of investigations have been during the years: electrocardiography of congenital heart disease; physiology of vallar heart disease and heart failure; ventricular function; spiral CT scan and MRI, in the last five years, in congenital and ischemic disease and heart failure. Clinical Cardiology has been his chief field of interest

Married to Savina since 1959, two daughters (Alessandra and Maurizia) professional music performers in Paris. Non-medical interests: music (piano player), foreign language (speaks ten foreign languages), history and philosophy.

After many years teaching Cardiology, doing research and caring patients, Dr. Dalla Volta wants to assure young Colleagues that Medicine can be the most noble profession activity, provided that you never forget to show (and feel) sympathy for the patients and try to prepare doctors loving this mission.
Dr. Garrett Gross

Dr. Gross graduated with his B.S. in Pharmacy in 1965 and his Ph.D. in Pharmacology from the University of Utah in 1971. He subsequently performed two postdoctoral fellowships, one at the Warner-Lambert Research Institute under the direction of Dr. Martin Winbury and the second at the University of Washington with Dr. Eric O. Feigl. Both of these eminent scholars stimulated Dr. Gross's interest in the control of coronary blood flow and in pharmacological mechanisms for reducing injury to the ischemic myocardium, an area in which he has been active for the past 33 years. Dr. Gross joined the faculty in Pharmacology and Toxicology at the Medical College of Wisconsin in 1973 and rose to the rank of Professor in 1980. He has been an active and continuously NIH-funded investigator at the Medical College of Wisconsin for the past 33 years. His major area of research concerns mechanisms by which endogenous substances released by the heart can either injure or protect the heart during ischemia and/or reperfusion and he has been a leader in understanding mechanisms by which the heart adapts itself to an ischemic insult, a phenomenon termed ischemic preconditioning (IPC). In this regard, Dr. Gross's laboratory was the first to demonstrate that an ATP-sensitive potassium channel (KATP channel) was a critical trigger and effector of IPC. This breakthrough has been repeated by a number of investigators and has stood the test of time as one of the key components of this remarkable cardioprotective phenomenon. This continues to be an active area of investigation in his laboratory and it is hoped that a pharmacological activator of this channel will be developed that is safe and efficacious and will be able to mimic the potent cardioprotective properties of IPC. In support of this concept, a potent opener of this channel, nicorandil, has been on the market in Japan and Europe for the treatment of stable angina since the 1990s and Dr. Gross's laboratory did much of the pioneering work on the development of this compound in the early 1980's. More recently, this was the first drug (IONA Trial) to demonstrate a long-lasting cardioprotective effect in patients with angina in a well-controlled clinical trial.

Along these same lines, Dr. Gross's was also the first laboratory to identify a role for endogenous opioids in mediating the cardioprotective effects of IPC in several animal models and that exogenous opioids such as morphine also possessed potent cardioprotective properties and that these effects were mediated via the action of opioids on both sarcolemmal and mitochondrial KATP channels. This finding has also led investigators in many other laboratories to study the role and mechanisms responsible for these potent cardioprotective properties of opioids.

These data suggest that it may be possible to use novel opioid compounds which lack CNS effects as cardioprotective agents in the future. Dr. Gross's laboratory also was the first to demonstrate that the cardioprotective effect of chronic morphine treatment persisted for 120 hours which suggests that this type of drug might be used prophylactically prior to cardiac surgery to put the heart in a protected state a day or two prior to and even after open heart surgery.

In his most recent work in which he was awarded the prestigious NIH MERIT Award, Dr. Gross has uncovered a new endogenous cardioprotective pathway which appears to be mediated by CYP 450 isoforms in the heart and that a product produced by CYP B-hydroxylases, 20-HETE, produces myocardial injury and that blocking the synthesis of or the receptor for this compound produces a marked reduction in infarct size in dog hearts. These data may lead to a new therapeutic target for drug development. Over the past 34 years Dr. Gross's work has resulted in approximately 380 full-length peer reviewed journal articles and reviews and 28 book chapters. Dr. Gross has been an invited speaker at more than 70 universities and pharmaceutical and biotechnology companies. He has been a consultant at over 20 pharmaceutical companies and has mentored 15 Ph.D. students and 10 postdoctoral fellows all of whom were funded by fellowships from the American Heart Association and the Pharmaceutical Manufacturers Association Foundation of America. Dr. Gross is a very active reviewer for all the top-notch cardiovascular journals including Circulation Research, Cardiovascular Research and JMCC and currently serves on the editorial board of 8 journals and has been an Associate Editor of the American Journal of Physiology (Heart and Circulatory) for the past 7 years. Dr. Gross is a Fellow of the American Heart Association, a Founding Fellow of the International Society of Heart Research and is a member of the American Society of Pharmacology and Experimental Therapeutics and the American Physiological Society. He served as member of the NIH Pharmacology Study Section for 4 years and continues to be an active ad hoc reviewer for the NIH on PPGs and RO1s related to the myocardial ischemia field. Recently, Dr. Gross has received a number of honors from various societies which include the John Foerster Distinguished Lecture (2005) awarded by the Institute of Cardiovascular Sciences in Winnipeg, the Keith Reimer Distinguished Lecture (2006) awarded by the International Society of Heart Research, The Distinguished Scientist Award (2006) awarded by the American Heart Association and the first Benedict Lucchesi Distinguished Lecture Award (2007) sponsored by the American Society of Pharmacology and Experimental Therapeutics.

Dr. Gross feels very fortunate to have been an active participant in a golden area of research in which many advances have made in discovering ways in which the heart can protect itself by releasing endogenous substances, the preconditioning phenomenon, and the more recent advances with gene therapy and cardiac regeneration, several areas that are still in their infancy but show great promise for future therapeutic advances. He is convinced that the best is yet to come.
A Historical Account of the Discovery of ANF and of the Endocrine Function of the Heart


The discovery of an endocrine link between the heart and the kidneys has its basis on the electron microscopic finding that the striated muscle cells of the cardiac atria in mammals are differentiated as both contractile and as endocrine cells. The demonstration of the fact the atria produce polypeptide hormones, was established with the discovery of Atrial Natriuretic Facto (ANF). ANF is the founder member of the ANF family of natriuretic peptides that have very important functions in the modulation of volume regulation and cardiovascular growth. The unfolding of this discovery, as many others, has a great deal of human content that often is lost in our technical writings. Hopefully, students and investigators just starting out will find inspiration (and consolation) in the informal account of the ANF discovery that follows.

When I arrived to the Pathology Department at Queen’s University in 1968, fresh from obtaining a Clinical Biochemistry degree from the Faculty of Chemical Sciences in Cordoba, Argentina, my supervisor, Sergio Bencosme, was interested in the functional morphology of the endocrine pancreas. As an aside, Bencosme had taken up the question of secretory-like differentiations found in atrial cardiocytes, a fact known since the early days of electron microscopy and manifesting itself most notably by the presence of storage granules known as “specific atrial granules” whose function was a mystery. He, and many other notables including George Palade then at the Rockefeller Institute in New York, could not advance past their morphological description. Others considered the atrial granules as an evolutionary remnant. I found myself unable to ignore a secretory phenotype making it a personal challenge to demonstrate that a combination of morphological and biochemical techniques would unravel the functional nature of the atrial granules. Perhaps I was influenced by the great endocrine work of Argentinean Nobel Prize laureate B. Houssay, who is an icon of academic excellence for anyone born in Argentina. And so the ANF saga began. It would take 12 years of investigations (with only one month of holidays) before the nature and function of the dual secretory-contractile nature of atrial cardiocytes would become apparent (For a review see (8)).

I began my studies on the possible secretory function of the heart by trying to isolate the atrial granules armed with the papers produced by Christian De Duve on isolation of subcellular organelles and the paper by Blascho on isolation of adrenal chromaffin granules. There was literature data that hinted that the atrial granules were a storage site for catecholamines but a careful read of the literature was not very convincing in that sense. At any rate, this was a hypothesis to test and this turned into my M.Sc. project. The isolation of the granules was particularly difficult because they were immersed in the great tangle of myofibrils and connective tissue that and homogenate of the heart muscle. Therefore, it took me two years and quite a few 20-60-rat ultracentrifugation runs to obtain the purified granules. Bigger animals (cow hearts were suggested many times) were of no use because there is an inverse relationship between the number of atrial granules found in atrial cardiocytes and the size of the animal. Since I had no biochemical marker for the granules, the most tedious job that I found was to look at every fraction by electron microscopy to see where the granules went with the many variations to the isolation technique (4). To this purpose I developed an electron microscopy embedding technique to deal with subcellular fractions. After many trials, I was able to isolate and purify the granules and proved by biochemical means that the granules did not contain catecholamines (3). This was success in one sense but it also meant that I had no hypothesis left to test.

I set out to develop techniques to specifically visualize the atrial granules at the light microscopic level. I reasoned that with such technique, one could correlate the distribution of the granules with histochemical reaction products. It helped me enormously the fact that, by intervention of Divine Providence I am sure, I had managed to twice end up working as a research assistant in Pathology Departments during my undergraduate years where I learned many histological techniques.

I developed the first method to specifically stain the granules at the microscopic level using lead-haematoxylin following a paper that my wife had found to stain cells in the pituitary gland (6). The stain aldehyde-fuchsin also provided a visualization of the granules. With these techniques at hand I carried out a whole battery of histochemical investigations (10). A number of cytochemical properties of the atrial granules were thus uncovered. These investigations would later help me isolate and purify ANF. For example, the poor stainability of the atrial granules following Bouin’s fixative (a fixative that contains acetic acid) suggested that the granules content was soluble in acetic acid. Indeed, ANF and BNP are highly soluble in acetic acid and it is the basis for extractants of these hormones. Altogether, these cytochemical studies plus the ones that I carried out later on as an independent investigator, provided evidence that the atrial granules stored a random coiled, basic polypeptide containing cystine and tryptophan. Autoradiographic studies with radio-labelled leucine showed that the granules content had high turnover in a manner similar to secretory cells (5). All of these properties were later confirmed by biochemical means following the isolation of ANF.

By this time (1973) I had finished my Ph.D. thesis, my first of our five children was born and we purchased our first home. I was then offered a position to continue at Queen’s, moving to the Pathology Laboratory at Hotel Dieu Hospital, an teaching hospital associated with Queen’s University, as an Assistant Professor of Pathology. I was to help develop research at this hospital and it was a leap of faith of the Chairman of Pathology, Nathan Kaufman, to put me there and for which I am very grateful. Years later, after the discovery of ANF, Nate reminded me that during my thesis defense I had guessed that the atrial granules, because of their location, might be involved in sensing changes in volume load. I had forgotten that.
A service-oriented hospital, Hotel Dieu was not the most propitious place for a young scientist. I was given an office, half a lab bench, an old incubator and a microscope to start. Mine was a windowless office in the basement, across from the autopsy room. The smell of formalin was a constant companion. Looking back, this isolation helped me in continuing with the goal of establishing the endocrine function of the heart.

My first grant application as an independent researcher to the Medical Research Council was on the status of the cardiac adrenergic innervation in heart failure. This is the reason why I have a publication on a new model for inducing heart failure in the guinea pig. This theme was really a safety valve in case the atrial granule business did not work out. As it turned out, the reverse occurred.

I secured funding from Heart and Stroke Foundation for continuation of my graduate studies on atrial granules but I knew that their patience was wearing thin on this theme. I also collaborated with Jack Kraicer of the Physiology Department at Queen’s on the morphology of the pars intermedia of the pituitary gland. My wife, who had started working with me, and I were able to define a system of canaliculi in this avascular gland using extracellular space markers. In the process, we discovered a new cell type for which my wife developed a silver impregnation technique to demonstrate it at the light microscopic level.

While the nature of the granule’s content appeared reasonably well defined by the histochemical studies, there was still no hint as to their function. However, we had now something that was not previously available. Namely, a stain that could demonstrate the granules at the light microscopic level and therefore, we could develop a quantitation procedure to assess changes in the number of granules after different experimental procedures using the light microscope. The difference between a morphometric procedure at the light microscopic level and procedures at the electron microscopic level is that the sample size is made much larger at the light microscopic level. This was particularly important for quantitation of atrial granules because of their irregular distribution in the atria and even within the same cell. We developed a morphometric procedure using the light microscopic staining developed during the histochemical studies using embedding in plastic to obtain uniformly thin sections of atrial tissue. Such procedure was then tested it statistically (1) and was later used to test claims that previous researchers had made regarding the ability of certain experimental manoeuvres to change the number of granules. There were many such claims, and counter claims and I tested most. I found unequivocal, statistically significant changes in the number of granules after some procedures known to alter water and electrolyte balance as previously suggested in electron microscopic studies by Bencosme and by P-Y Hatt (2). The difference afforded by the light microscopic quantitation of granules was that one could be confident that the changes were not the result of biased sampling and therefore, one could really commit one’s time to further the study without the feeling of being wasteful.

The hypothesis thus developed was that the atria produced and stored a polypeptide that helped regulate water and electrolyte balance given the nature of the contents revealed by histochemistry and the changes in the number of granules revealed by the morphometric technique after procedures known to alter water and electrolyte balance. I thought that the easiest way for a cardiac hormone to modify water and electrolyte balance was by targeting the prominent role of the kidneys in maintaining water and electrolyte homeostasis. Besides, the atria were in an ideal spot to sense changes in venous return. Looking for a bioassay for diuretic substances, I found that Harald Sonnenberg of the Department of Physiology at the University of Toronto, whom I did not know, was searching for a natriuretic hormone and had a rat bioassay for that purpose. I phoned him and related to him my quest and hypothesis.

Since the existence of atrial granules was not widely known, even by morphologists, it was specially generous of Harald to accept my invitation “to take a shot in the dark”. He invited me to give a seminar in Toronto and we agreed that I would send him atrial extracts. The first extracts were, in fact, atrial granule extracts that contained a high concentration of potassium chloride due to the composition of the solutions used for isolation. This promptly killed the bioassay rats upon injection. I then more or less supplicated Harald to be patient and to please try just crude extracts of atria, and of ventricles as a control, prepared in simple phosphate-buffered saline.

Some weeks went by and then, to my unbelieving ears, Harald phoned me saying that the injection of atrial extracts produced a diuresis and natriuresis that was immediate and incredibly strong, just like furosemide. Always a worrier, I started to wonder about what contamination would produce such effects. We repeated the experiments many times in my lab and the results were equally impressive. Also, proteinase destroyed the activity, which went right along with the hypothesis that the atrial granules contained a polypeptide hormone.

The potential importance of the finding prompted us to send our findings to the prestigious Journal of Clinical Investigation. It was tersely rejected in a letter dated May 28, 1980, given that the finding “was not thought to be suitable for publication...” Because I had disclosed the findings previously at a meeting of the Canadian Society for Clinical Investigation meeting, we decided to publish the findings as quickly as possible. For that reason it was sent to Life Sciences where it was quickly accepted and published in 1981 (7). By 1983 the first publications on ANF from other centers started to appear. Not a single lab failed to confirm our findings given that the natriuretic and diuretic activities of atrial extracts were so powerful that nothing short of a dead bioassay rat could stop such action.

The article in Life Sciences spurred a flurry of activity and went on to become a Citation Classic as qualified by the Institute of Scientific Information. Needless to say that the researchers in the hypertension field were ready to exploit the finding of a hormone that was diuretic, natriuretic and hypotensive. It is of interest to note the different reactions by different groups of investigators. Some invited me to present my work and recognized the discovery in one way or another. Others embarked in a furious research pace on ANF and in a public relations campaign; some including televised speeches, to convince the world that they had discovered ANF. It was never clear to me how they planned to claim a discovery for which we had an indisputable three-year precedence in publishing. I guess that a discovery that came from a basement of an obscure hospital was deemed easy pray. At any rate, it looks that all discoveries follow the same libretto. The Japanese authors, although they also invented a new name (ANP) and thus disregarded an international nomenclature agreement reached in New York and still existing, did truly contribute to the natriuretic peptide field by demonstrating the occurrence of BNP and CNP based on the ANF discovery.
Our laboratory also was the first to isolate, purify and sequence ANF (9,12,13). The way that this was accomplished was not less heroic than the 12 years of work preceding the ANF discovery. It was very opportune for me to find in the US a company that provided us with rat atria. In total, around 200,000 rat atria were used. It was also fortunate that the techniques for isolation of peptides by HPLC were coming into use. The only problem was that I did not have an HPLC. The Clinical Laboratory in our hospital, however, had just purchased one to do patient’s theophylline in serum. Luckily, I was put in charge of that technique so it was not very noticeable that I came during the night to re-configure the machine and fitted it with a chromatographic column to purify peptides.

Three people essentially did the isolation and purification of ANF in my laboratory: my wife would extract the atria, I would purify the extracts and a technician would test the different fractions obtained during purification in the bioassay rat. No other resource or person was involved in this effort.

Once the peptide was purified to chemical homogeneity, my next problem was to sequence it. The only person at Queen’s involved in amino acid analysis and protein sequencing was Geoff Flynn to whom I offered collaboration. We had various false stars due to antiquated equipment, both in the amino acid analysis and in the sequence results. The problems were resolved when we obtained funding from the government of Ontario to purchase a gas phase sequencer and thus we were the first laboratory to produce a sequence in 1983 (13). The Japanese workers produced the human sequence the following year.

Students often ask for advice to succeed in research and my standard answer is: “Have a dream, don’t think small, work hard and believe in yourself” I finish this in my mind with: “..and pray that you are right”

Reference List
State-of-the-brain-and-heart: Homo Obesus Bulgaricus
Bulgaria, a country in the epicenter of global healthquake


When someone declared that life is an evil, Diogenes said:
Not life itself, but living ill.

Today, it is increasingly known that adipose (fat) tissue is a very active endocrine organ producing more than 100 types of biologically active proteins, collectively designated adipokines (1-3). Adipotopography (fat mapping) is an emerging sub-field of adipobiology, investigating the localization and amount of adipose tissue in the human’s body (4, also Dr Jimmy Bell - personal communication, see below).

The present state-of-the-brain-and-heart view deals with feeding behavior, food culture, and obesity-related cardio-metabolic diseases, the major recent enemies of human brain and heart health, especially targeting Bulgarians.

We recently have introduced the term Homo obesus (Man the obese/fat) (3,5) as a novel feature of H. sapiens, H. informaticus, H. globalus.

H. obesus derives from a dysbalance between genes, lifestyle/quality of life (QOL), and environment. Mutations in genes and their on-off switching are now well-accepted as a basic concept of the evolutionary theory of Charles Darwin, also
neu-Darvinism of modern synthesis. Such a game of mutations ensures survival and reproduction of species throughout extremely difficult periods of time, including famine. To be ready to cope the next shortage of food, our progenitors of hunter-gatherer’s era of H. ergaster and H. erectus, in relaxing periods of their life, have hedonistically eaten ad libitum, as an adaptation reaction, that is, accumulating calories, which will be used during the next famine. In this era, to become fatter meant to better cope such a hungerins. However, the genes that governed a “thrifty” feeding behavior during famine-feast cycling, in the last 20-30 years, when food availability is flourished, predispose to overweight and obesity. Briefly, these same thrifty genes became obesegenic in the years of macdonalization of our food culture. Today’s man takes a surplus amount of food, believing in his evolutionary lessons of “the fatter, the better”. Since the anticipated famine does not occur and because of less physical activity, the stored calories are not expended, and thus accumulated in fat tissue, hence H. obesus. In effect, ac-cumulation of fat is an ac-cultural (transcultural) phenomenon, including a fast-food/macdonalized globalisation of our food culture (see 6-8 for Yukio Yamori’s data of Japanese emigrated to Brazil - they live 10 year less than those remaining in Japan). At a basic research level, one may wonder about molecular, particularly adipokine profile of both Israeli fat sand rats (Psammomys obesus) and Atlantic bigeye tuna (Tunnus obesus).

“I am a citizen of the world” – this statement of H. obesus is a copy of words of Diogenes (412-323 BC). Obviously, obesity is a pandemic event, and H. obesus is not living in Bulgaria only. Atherosclerotic and hypertensive BH diseases are the world’s greatest killers of annually more than 19 million lives. Additionally, rheumatic heart disease kills 15.6 million people worldwide, including 2.4 million children, mainly in Africa.

According to the World Health Organization’s reports, 1 billion people worldwide are overweight, at least 300 million of whom are obese. In Europe (population of about 700 million) there are 130 million obese and 400 million overweight people, that is, a total of 530 million fat Europeans, who remain a major health target for the European Union, including Bulgaria, being a member since 1 January 2007.

Of note, about 80% of the world’s brain-and-heart (BH) disease burden occurs in low-and middle-income countries. Because people at low socioeconomical scale are experiencing unhealthy lifestyle, due to a shortage of both money and health education (many Bulgarians belonging to that category of people). However, the poverty itself is not a sin, it is a big mistake of the state allowing poverty to exist and not paying attention to QOL that should also be embodied into the list of human rights.

Japanese experience in BH disease, particularly stroke, may indeed serve a role model for predictive and preventive medicine. In the 1960’s, Japanese died from stroke even more often than Bulgarians. However, due to the progress in Japanese basic research in hypertension and stroke and its implication in the prevention, stroke mortality was significantly reduced in Japan (6-8). Moreover, Japanese women are enjoying an average life span of 85 years, and men - 78 years, thus being among the longest life span worldwide.

Since 1986, one of us (GNC) has also been participating in this Japanese medical progress, used to work for the Japan Stroke Prevention Center in Izumo, Shimane Medical University and now, another of us (DK), is working for the International Center for Research on Primary Prevention of Cardiovascular Diseases chaired by the famous Yukio Yamori senn-sei, in Kyoto.

Bulgaria is among the leading country worldwide in mortality from BH diseases in the last 3-4 decades. From less than 8 million, about 75,000 Bulgarians die each year from either stroke or myocardial infarction; each third Bulgarian is hypertensive; about 25 percent of children are overweight or obese and more than 10 percent are hypertensive and/or diabetic. Whateversoever communism (1944-1989) or democracy (1990- ), Bulgaria is a country in the epicenter of global BH healthquake.

A combination of a hight mortality and a low birth rate, accompanied by a low QOL, primitive health culture and an increasing emigration, places Bulgaria in a severe demographic crisis (9). Hence, most of Bulgarians today should be considered

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“malcitizens”, i.e., patients having at least one of QOL-related diseases. Specifically, H. sanus (Man the healthy) must no longer be ignored in Bulgaria. Physicians, scientists and patients must all together increasingly press the politicians to invest more financial support to predictive and preventive medicine, also basic biomedical research. To wait donation from the Foundations of Bill and Melinda Gates and Bill Clinton is not a realistic strategy. This may indeed arrive from the European Union but, at government levels, must be properly (and honestly) utilized.

Recent experimental and epidemiological studies indicate that calorie restriction and moderate drinking of red, resveratrol-rich, wine (5,10,11), and physical activity may promote healthy longevity, the major goal of both medicine and society. But not of Bulgarian politicians! In the same time, in advanced countries, both medics and politicians are thinking of how to make their citizens “longivitarians”, a term recently emerged.

Further, everyone should also be informed about a H. obesus’ relative, TOFI (Thin Outside, Fat Inside), recently described via MRI scanning by Dr Jimmy Bell, head of the Molecular Imaging Group at Hammersmith Hospital, Imperial College, London, UK. Note, TOFI is a specific, “invisible” phenotype of H. obesus (see Table, also reference 4).

**Teleologically**, our common goal must be (re)creation of H. sanus. “Thinking globally, acting locally” (quoting Rene Dubot), we may indeed achieve this goal. Today, the European Union proclames building society and economics based on the tribology of education, science and innovations. This may help each of us to, at long last, stay sane, and not longer being obese.

Because living healthy and well-educated may indeed ensure Eudemonia, that is, “highest good life” in sense of Aristotelian ethics and logic. Applying CR (calorie restriction) and boosting our CR (creative resources) in our lifestyle could hopefully contribute to the efforts in achieving that goal.

### Table. Adipotopography (fat mapping) – variations+

<table>
<thead>
<tr>
<th>TOFI**</th>
<th>thin outside, fat inside</th>
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<tr>
<td>TOTI***</td>
<td>thin outside, thin inside</td>
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<tr>
<td>FOFI*</td>
<td>fat outside, fat inside</td>
</tr>
<tr>
<td>FOFI**</td>
<td>fat outside, thin inside</td>
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</tbody>
</table>

+ The number of asterisks, as for hotels, indicates quality, here – the QOL in BH health. Hence, stay TOTI!

References


World Heart Day

Cardio-vascular diseases - including heart attacks and strokes - are the world’s largest killer, claiming 17.5 million lives a year. World Heart Day was established to create public awareness of risk factors for heart disease and stroke and to promote prevention.

There are 155 million overweight and obese children globally. Parents can influence and help children in reducing major risk factors for heart disease and stroke - such as controlling weight by healthy eating and doing regular physical activity. That is why this year’s World Heart Day (September 30, 2007) focuses on the theme “Team Up for Healthy Hearts”.

In partnership with WHO, the World Heart Federation organized activities in more than 100 countries. The activities included health checks, organized walks, runs and fitness sessions, public talks, stage shows, scientific forums, exhibitions, concerts, carnivals, and sports tournaments.

For more information, visit: http://www.world-heart-federation.org/what-we-do/world-heart-day/about-world-heart-day
“When I first told my friends I was traveling to Jordan, they thought I was crazy. When I then told them I was bringing them along, they tried everything they could to come up with an excuse not to go. I dragged them there, and then a funny thing happened. Five days later, they tried everything they could...to stay. They discovered what I already knew— that Jordan is one of the safest, most hospitable places I know. I may live in America, but in Jordan, I am always welcomed home.”

These words were written by Peter Greenberg, Travel Editor, Today’s Show, NBC News

Yes Jordan is the safest place in the middle and foreign people can walk freely all over Jordan. We receive large number of tourists from all over the globe. They spend memorable days for all their life.

God repeatedly designated Jordan as a land of peace and refuge, where Ruth, Elijah, David, Jesus, John the Baptist and the first Christian communities, among others, found safety and peace. Most of the great biblical prophets journeyed from the east bank of the Jordan River to the west, symbolically moving from the “wilderness” where men and women are tested, to the Holy Land, the Kingdom of God. Among these leading figures whose journeys took them from the east to the west banks of the Jordan River were Abraham, Jacob, Moses, Joshua, Elijah, John the Baptist and Jesus.

Most of the holy sites in Jordan where the biblical prophets performed miracles or reached out to ordinary people are identified, excavated and easily accessible to visitors today. New sites are discovered every year. Religious pilgrims and visitors to Jordan often can visit archaeological excavations and share in the excitement of identifying ancient remains of places. For 10,000 years travelers have marveled the majestic archaeological sites and natural wonders of hospitable Jordan. The abundance of unique sights across the land is only but a reflection of the rich culture heritage of the Kingdom. Visitors are enchanted, mystified and captivated by the famous rose-red Nabatean city of Petra; Greco-Roman temples and cities; Crusader and Umayyad castles; the spectacular deserts made famous by Lawrence of Arabia; innumerable biblical sites identified with Jacob, Moses, Elijah, John the Baptist and Jesus Christ; the Red Sea and the Dead Sea; and the capital city of Amman- a fascinating mixture of ancient and modern contrasts.

So Jordan offers venues that cannot be duplicated anywhere in the world for special events and theme parties.

We invite you to browse through (Jordan Tourism Board of North America: www.seejordan.org ) and learn all about the astounding sites in the country, including the capital Amman, the magnificent Nabatean city of Petra, the spectacular Greco-Roman ruins of Jarash, the desert castles, Lawrence’s famous Wadi Rum, and many other historical and impressive sites throughout the Kingdom.

Experience the biblical Jordan visiting Bethany - Beyond - Jordan where John the Baptist baptized Jesus, Mount Nebo where Moses stood one day, Madaba the City of Mosaics and various other sites of this eastern Holy Land.

We highly encourage you to come and see the beauty of the Kingdom’s treasures and experience the splendor that has dazzled visitors for centuries.

The ancient city of Petra is one of Jordan’s national treasures and by far its best known tourist attraction. Located approximately three hours south of Amman, Petra is the legacy of the Nabataens, an industrious Arab people who settled in southern Jordan more than 2000 years ago. Admired then for its refined culture, massive architecture and ingenious complex of dams and water channels, Petra is now a UNESCO world heritage site that enchants visitors from all corners of the globe. Much of Petra’s appeal comes from its spectacular setting deep inside a narrow desert gorge. The site is accessed by walking through a kilometre long chasm (or SEEQ), the walls of which soar 200 metres upwards. Petra’s most famous monument, the Treasury, appears dramatically at the end of the seeq. Used in the final sequence of the film “Indiana Jones and the Last Crusade”, the towering facade of the Treasury is only one of myriad archaeological wonders to be explored at Petra. Various walks and climbs reveal literally
hundreds of buildings, tombs, baths, funerary halls, temples, arched gateways, colonnaded streets and haunting rock drawings - as well as a 3000 seat open air theatre, a gigantic first century Monastery and a modern archeological museum, all of which can be explored at leisure. A modest shrine commemorating the death of Aaron, brother of Moses, was built in the 13th century by the Mamluke Sultan, high atop mount Aaron in the Sharah range.

Also within the area is Mount Nebo, one of the most revered holy sites of Jordan and the place where Moses was buried. A small Byzantine church was built there by early Christians, which has been expanded into a vast complex. During his visit to Jordan in 2001, the Late Pope John Paul II held a sermon here that was attended by some 20,000 faithful. Stand on the platform in front of the church and admire the view. It overlooks the Jordan Valley and the Dead Sea, across to the rooftops of Jerusalem and Bethlehem and is absolutely breathtaking. Just 30 km from Amman, along the 5,000-year-old Kings’ Highway, is one of the most memorable places in the Holy Land. After passing through a string of ancient sites, the first city you reach is Madaba, known as the “City of Mosaics”.

Best known for its spectacular Byzantine and Umayyad mosaics, Madaba is home to the famous 6th century Mosaic Map of Jerusalem and the Holy Land. With two million pieces of vividly colored local stone, it depicts hills and valleys, villages and towns as far as the Nile Delta.

The Madaba Mosaic Map covers the floor of the Greek Orthodox Church of St. George, which is located northwest of the city centre. The church was built in 1896 AD, over the remains of a much earlier 6th century Byzantine church. The mosaic panel enclosing the Map was originally around 15.6 X 6m, 94 square meters, only about a quarter of which is preserve.

Other mosaic masterpieces found in the church of the Virgin and the Apostles and in the Archaeological Museum, depict a rampant profusion of flowers and plants, birds and fish, animals and exotic beasts, as well as scenes from mythology and the everyday pursuits of hunting, fishing and farming. Literally, hundreds of other mosaics from the 5th through the 7th centuries are scattered throughout Madaba’s churches and homes.

A close second to Petra on the list of favorite destinations in Jordan, the ancient city of Jarash boasts an unbroken chain of human occupation dating back more than 6,500 years. Conquered by General Pompey in 63 BC, it came under Roman rule and was one of the ten great Roman cities, the Decapolis League.

The city’s golden age came under Roman rule, during which time it was known as Gerasa, and the site is now generally acknowledged to be one of the best preserved Roman provincial towns in the world. Hidden for centuries in sand before being excavated and restored over the past 70 years, Jarash reveals a fine example of the grand, formal provincial Roman urbanism that is found throughout the Middle East, comprising paved and colonnaded streets, soaring hilltop temples, handsome theatres, spacious public squares and plazas, baths, fountains and city walls pierced by towers and gates.

This is a stupendous, timeless place, virtually untouched by humanity and its destructive forces. Here, it is the weather and winds that have carved the imposing, towering skyscrapers, so elegantly described by T.E. Lawrence as “vast, echoing and god-like”. A maze of monolithic rock-scapes rise up from the desert floor to heights of 1,750 metres creating a natural challenge for serious mountaineers. Hikers can enjoy the tranquility of the boundless empty spaces, explore the canyons and water holes to discover 4000 year old rock drawings and the many other spectacular treasures this vast wilderness holds in store.

Dead Sea
Without doubt, the world’s most amazing place, the Jordan Rift Valley is a dramatic, beautiful landscape, which at the Dead Sea, is over 400 metres (1,312 ft.) below sea level. The lowest point on the face of the earth, this vast, stretch of water receives a number of incoming rivers, including the River Jordan. Once the waters reach the Dead Sea they are land-locked and have nowhere to go, so they evaporate, leaving behind a dense, rich, cocktail of salts and minerals that supply industry, agriculture and medicine with some of its finest products.

The leading attraction at the Dead Sea is the warm, soothing, super salty water itself – some ten times saltier than sea water, and rich in chloride salts of magnesium, sodium, potassium, bromine and several others. The unusually warm, incredibly buoyant and mineral-rich waters have attracted visitors since ancient times, including King Herod the Great and the beautiful Egyptian Queen, Cleopatra. All of whom have luxuriated in the Dead Sea’s rich, black, stimulating mud and floated effortlessly on their backs while soaking up the water’s healthy minerals along with the gently diffused rays of the Jordanian sun.
Myocardial Protection From Lab to Man

The Symposium will focus on recent advances in Myocardial Research such as Stem Cells and Ischemic Preconditioning which have made great strides towards Heart Health

Speakers: Sir Magdi Yacoub (UK), Naranjan Dhalli (Canada), James Downey (USA), Jamil Tajik (USA), Pawan Singal (Canada), Nabil El-Shariff (USA), Derek Yellon (UK), Gerd Heusch (Germany), Ivan Berkowitz (Canada), Gary Lopaschuk (Canada), Grant Pierce (Canada), Rakesh Kukreja (USA), Max Lab (UK).